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FORM PTO 1390 (REV 11-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER REGIM-012
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371			U.S. APPLICATION No. (If known, see 37 CFR 1.5) 10/088851
INTERNATIONAL APPLICATION NO. PCT/FR00/02600	INTERNATIONAL FILING DATES 20 September 2000	PRIORITY DATE CLAIMED 22 September 1999	
TITLE OF INVENTION USE OF A PLANT OIL PRODUCT AS AN AGENT FOR INCREASING THE SYNTHESIS OF SKIN LIPIDS			
APPLICANT(S) FOR DO/EO/US Philippe Msika and Antonie Piccirilli			

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

- ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
- ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing 35 U.S.C. 371
- ☒ This is an express request to begin national examination procedures (35 U.S.C. 371 (f)). The submission must include items (5), (6), (9) and (21) indicated below.
- ☒ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
- ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
 - ☐ is attached hereto (required only if not communicated by the International Bureau).
 - ☒ has been communicated by the International Bureau.
 - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
- ☒ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
 - ☒ is attached hereto.
 - ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
- ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - ☐ are attached hereto (required only if not communicated by the International Bureau).
 - ☐ have been communicated by the International Bureau.
 - ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - ☒ have not been made and will not be made
- ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
- ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). (Executed)
- ☒ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

- ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
- ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
- ☐ A **FIRST** preliminary amendment.
- ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
- ☐ A substitute specification.
- ☐ A change of power of attorney and/or address letter.
- ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
- ☒ A second copy of the published international application under 35 U.S.C. 154(d)(4).
- ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
- ☒ Other items or information: Copy of International Preliminary Examination Report w/annexes (in French & English)

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SIGNATURE.

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Use of a plant oil product as an agent for increasing
the synthesis of skin lipids

5 The present invention relates to the use of a plant oil
product as an agent for increasing the synthesis of
skin lipids, especially the lipids of the epidermal
skin barrier, in or for the preparation of a cosmetic,
pharmaceutical or dermatological composition. The
invention also relates to a method for cosmetic
10 treatment with a cosmetic, pharmaceutical or
dermatological composition for increasing the synthesis
of skin lipids, especially the lipids of the epidermal
skin barrier, and to the use of the plant product as a
food additive.

15 The skin consists mainly of three layers: the
epidermis, the dermis and the hypodermis.

20 The outermost layer, the epidermis, is characterized by
organization into strata corresponding to a state of
increasing differentiation of the keratinocytes, from
the deepest region (stratum basale) to the outermost
region (stratum corneum) within which anuclear elements
(corneocytes) are included in a multilamellar
25 extracellular lipid structure, the intercorneocytic
cement, responsible for the skin's water barrier
function and for protection against external attack.

30 The lamellar bodies, or Oddland bodies, secreted by the
stratum granulosum, a layer intermediate between the
stratum basale and the stratum corneum, contain
cholesterol, phospholipids and glucosylceramides and
also selective hydrolases. These enzymes convert
phospholipids and glucosylceramides into free fatty
35 acids and ceramides which form, with cholesterol and
cholesteryl sulfate, the intercellular lamellar
bilayers of the stratum corneum. Ceramides participate
predominantly in the formation of the barrier formed by

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the stratum corneum and in regulating water flow by unifying the lamellae. A large reduction in the content of/and the type of ceramide is especially observed in atopic dermatitis (or atopic eczema) or in acne (ceramide 1) and in dry skin and pruritus in the elderly. Cholesteryl sulfate, via a specific sulfatase, is in equilibrium with cholesterol (leaflet-fluidizing agent). They play an important role in corneocyte cohesion and thus in skin desquamation, and also in skin comfort.

An impairment in this skin barrier caused by external attack (UV radiation, wind, cold, detergents, etc.), by the natural and inexorable phenomenon of aging and/or by pathological or nonpathological dysfunctions (sensitive, irritated or reactive skin) is manifested in a disruption in the epidermal homeostasis which it is desirable to be able to prevent and/or treat both cosmetically and pharmaceutically and especially dermatologically.

For example, the article by Ruby Ghadially et al., "Decreased Epidermal Lipid Synthesis Accounts for Altered Barrier Function in Aged Mice", The Journal of Investigate Dermatology, vol. 106, no. 5, May 1996, teaches that an impaired skin barrier and also an abnormal content of lipids in an aged mouse epidermis can be explained by an impaired synthesis of the epidermal lipids.

There is thus a need to be able to stimulate the synthesis of the skin lipids, especially the lipids of the epidermal skin barrier, so as to be able in particular to restore the skin barrier function of the epidermis and/or to combat various skin disorders associated with a reduction in the synthesis of skin lipids, especially the lipids of the epidermal skin barrier.

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It has now been found, entirely surprisingly and unexpectedly, that the use of certain plant oil products makes it possible advantageously to synthesize skin lipids, especially lipids of the epidermal skin barrier.

One subject of the present invention is thus the use of at least one plant oil product chosen from the group consisting of oil distillates of plant oil, unsaponifiable materials from plant oil, furan lipids of plant oil and mixtures thereof as agents for increasing the synthesis of skin lipids, especially the lipids of the epidermal skin barrier known to those skilled in the art, like those mentioned above, in or for the preparation of a composition containing a cosmetically, pharmaceutically or dermatologically acceptable medium.

In particular, the use according to the invention is characterized in that the skin lipids are chosen, inter alia, from the epidermal lipids of the group consisting of cholesterol, cholesteryl sulfate, ceramides 1 and 2 and mixtures thereof.

Among the plant oils that may be used, mention may be made in particular of sunflower oil, palm oil, palm kernel oil, coconut oil, grapeseed oil, black mustard oil, poppyseed oil, karite butter oil, sweet almond oil, soybean oil, avocado oil, groundnut oil, cotton oil, sesame oil, olive oil, corn oil, cocoa bean oil, castor oil, behen oil, flax oil, rapeseed oil, annatto oil, wheatgerm oil, safflower oil, walnut oil, hazelnut oil and turnipseed oil.

According to the invention, the expression "oil distillate of a plant oil" means a plant oil which has been subjected to a step of concentration of its unsaponifiable material.

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preferably as follows:

- temperature from 230 to 250°C;
- pressure from 10^{-3} to 10^{-2} mmHg;
- degree of distillation of about 5 to 10%
by mass.

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The degree of distillation may be defined as follows:
it is the mass ratio, relative to 100%, of the mass of
the distillate to the sum (mass of the distillate +
mass of the residue).

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The distillate thus obtained, i.e. the oil distillate
of sunflower oil, has an unsaponifiable material
content of between about 6% and about 10% by weight,
the remaining part being composed of sunflower oil
triglycerides.

15

The unsaponifiable material of a plant oil which may be
used according to the invention is preferably chosen
from the group consisting of the unsaponifiable
material of avocado oil and the unsaponifiable material
of soybean oil, and mixtures thereof.

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Comparison of the unsaponifiable material contents of
various plant oils - soybean, cotton, coconut, olive
and avocado - shows a very large amount of
unsaponifiable material in avocado oil, obtained by
extraction according to various known processes.
Typically, the contents obtained range from 2 to 7% of
unsaponifiable material in avocado oil, compared with
0.5% in coconut oil, 1% in soybean oil and 1% in olive
oil.

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The higher content of unsaponifiable material in
avocado oil compared with the other plant oils such as
mentioned above is explained in particular by the
presence, in the unsaponifiable material of avocado
oil, of constituents which are not generally found in

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Thus, the unsaponifiable material of avocado oil used according to the invention may be obtained from the

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fresh fruit, but, preferably, the unsaponifiable material of avocado is prepared from fruit that has been heat-treated beforehand, prior to extracting the oil and saponifying it, as described in patent
5 FR-2 678 632.

This heat treatment consists of a controlled drying of the fruit, which is preferably fresh, for at least four hours, advantageously at least 10 hours, preferably
10 between about 24 and about 48 hours, at a temperature preferably of at least about 80°C and preferably between about 80°C and about 120°C.

Mention may also be made of the process for preparing
15 the unsaponifiable material of soybean oil, obtained from a concentrate of unsaponifiable material of soybean oil. The said concentrate of unsaponifiable material is prepared by molecular distillation according to a process such as the one described for
20 lupin oil in patent application FR-A 762 512, but adapted to soybean oil. In this process, the soybean oil is distilled in a molecular distillation device of centrifugal type or of scraped-film type, at a temperature of between about 210°C and 250°C and under
25 a high vacuum of between 0.01 and 0.001 millimeters of mercury (i.e. 0.13 to 1.3 Pa). The distillate obtained has an unsaponifiable material content of between 5% and 30% by weight and thus constitutes a concentrate of unsaponifiable material of soybean oil. This
30 concentrate is then saponified according to a conventional saponification process, in the presence of ethanolic potassium hydroxide. The mixture obtained is extracted with dichloroethane in a counter current column. Finally, the solvent is removed from the
35 solvent phase by passing it through a falling-film evaporator in order to recover the unsaponifiable material of soybean.

20 According to the invention, the expression "furan
lipids of a plant oil" means compounds comprising a
linear C₁₁-C₁₉ hydrocarbon-based main chain, which is
saturated or comprises one or more ethylenic or
acetylenic unsaturations, and a 2-furyl group at one of
25 its ends. Among the furan lipids of a plant oil which
may be used according to the invention, the ones most
particularly preferred are the furan lipids of avocado.
This is because avocado comprises specific lipids of
furan type, the main component of which is a linoleic
30 furan;



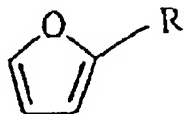
35 The furan derivatives of avocado oil have been
described in particular in Farines, M. et al, 1995, J.

Specifically, it is known that these furan lipids are metabolites of compounds that are initially present in the fruit and leaves and which, under the effect of heat, dehydrate and cyclize to give furan derivatives.

CC(=O)OCC(O)C(=O)CCCCCCCC/C=C\CCCC/C=C\CCCC

precursor P1H7'

According to the invention, the expression "furan lipids of avocado" in particular means the components corresponding to the formula:



The known processes for obtaining these specific compounds from avocado fruit or from avocado fruit oil come down to either preparative chromatography or industrial processes for obtaining these furan lipids as a mixture with the other unsaponifiable compounds of

5 A novel process for preparing these furan lipids of
avocado was the subject of a patent application filed
this very day. It consists essentially of a process for
selectively extracting the furan lipids of avocado,
characterized in that it comprises the steps consisting
10 in preparing an unsaponifiable material of avocado and
then in subjecting the unsaponifiable material of
avocado to a step of molecular distillation using
temperature means regulated for a temperature of
between 100°C and 160°C and pressure means regulated
15 for a pressure of between 10^{-3} mmHg and 5×10^{-2} mmHg.

According to the invention, the plant oil product as described above is used in a proportion of between 25 about 0.01% and 100% by weight and preferably between about 0.5% and about 10% by weight relative to the total weight of the composition.

35 In particular, this medium may be an oily solution, a water-in-oil emulsion, an oil-in-water emulsion, a microemulsion, an oily gel, an anhydrous gel, or a

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dispersion of vesicles, microcapsules or microparticles.

5 The composition for the use according to the invention is preferably suitable for administration by topical application.

10 The advantageous effect of increasing the synthesis of the skin lipids, especially the lipids of the epidermal skin barrier, makes it possible to prevent and/or treat, in other words allows the treatment of, impairments of the skin barrier formed mainly by the epidermal layers of the stratum corneum and the stratum granulosum as explained above.

15 Thus, the use according to the invention is characterized in that the composition is intended for treating dry skin and skin that has been subjected to actinic radiation, especially UV radiation, such as
20 solar radiation or radiation from a UV lamp, for example during an artificial tanning session.

The use according to the invention is also characterized in that the composition is intended for
25 treating ichthyosis, acne, xerosis, atopic dermatitis (or atopic eczema), skin disorders associated with a reduction in the content of skin lipids, especially the lipids of the epidermal skin barrier, and disorders of corneocyte cohesion and of desquamation of the skin,
30 sensitive, irritated and reactive skin, and pruritus.

A subject of the present invention is also a method for cosmetic treatment disorders associated with aging of the skin, neighboring mucous membranes and/or
35 integuments, characterized in that a composition containing at least one plant oil product in a cosmetically acceptable medium as described above is applied to the skin, neighboring mucous membranes

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and preferably between about 0.5% and about 10% by weight relative to the total weight of the composition.

Finally, another subject of the invention is the use of
5 at least one plant oil product, as described above, as an additive in a food for humans and/or animals.

This food use is preferably characterized in that the plant oil product is present in the food in a
10 proportion of between about 0.1% and about 20% by weight relative to the total weight of the food.

The examples which follow are intended to illustrate the present invention and should not in any way be
15 interpreted as possibly limiting its scope.

Unless otherwise specified, the percentages indicated in the examples below are percentages by weight.

20 **Example 1: Preparation of plant oil products and their use according to the invention in the form of oil-in-water emulsions**

The following compositions 1.1 to 1.3 and the placebo
25 composition were each prepared in the following way:

The constituent components of the aqueous phase (water and glycerol) are placed in a water bath at 75°C. The components of the fatty phase, except for the Sepigel
30 305, the Silicone SF 1202 and the plant oil product (prepared below, respectively, under the names "sunflower oil distillate 1", "unsaponifiable materials 1" and "lipids 1"), are placed in a water bath at 75°C. Just before performing the
35 emulsification, the Silicone 1202 and the respective plant oil product are added to the fatty phase. The emulsion is then prepared by turbomixing at low speed by incorporating the fatty phase into the aqueous

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phase. When the preparation has reached a temperature of 60°C, the Sepigel 305 is added with high-speed turbomixing. The composition is then allowed to cool at rest to room temperature, before being used in the tests described below.

1.1) Composition 1.1: Use of an oil distillate of sunflower oil

A sunflower oil distillate is prepared by molecular distillation, in a molecular distillation machine of centrifugal type, of a commercial food-grade sunflower oil. The distillation conditions are as follows:

- temperature 220°C;
- pressure of 10^{-3} mmHg;
- degree of distillation: 6/7% by mass
- feed rate: 18 kg/h

The distillate obtained, sunflower oil distillate, has a content of unsaponifiable materials of about 6.2% by weight, the remaining portion being composed of sunflower oil triglycerides. The oil distillate thus obtained is referred to as "sunflower oil distillate 1".

Composition 1.1 (INCI formula)	% (by weight)
Aqueous phase	
Water	67.3
Glycerol	4
Fatty phase	
Sorbitan tristearate	1.85
PEG-40 stearate	3.15
Silicone SF 1202	3
Cetiol Oe	1
Petroleum jelly codex	2.5
Glyceryl stearate	6

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Decyl pentanoate	3
Sunflower oil distillate 1	2
Beeswax	3
PEG-2 stearate	1
C12-15 alcohol benzoate	1
Phenonip	0.7
Sepigel 305	0.3
TOTAL	100%

1.2) Composition 1.2: Use of a mixture of an unsaponifiable material from avocado and from soybean

5 The mixture of unsaponifiable materials from avocado
oil and from soybean oil as sold by the company
Laboratoires Pharmascience under the name "Piascledine
300®", which consists of a mixture of 33.3% by weight
of unsaponifiable materials from avocado and 66.6% by
10 weight of unsaponifiable materials from soybean,
relative to the total weight of the mixture (the
remaining 0.1% consisting of colloidal silica and
butyl- hydroxytoluene) is used. This mixture is
referred to hereinbelow as "unsaponifiable materials
15 1".

Composition 1.2 (INCI names)	
Aqueous phase	
Water	67.3
Glycerol	4
Fatty phase	
Sorbitan tristearate	1.85
PEG-40 stearate	3.15
Silicone SF 1202	3
Cetiol Oe	1
Petroleum jelly codex	2.5

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Glyceryl stearate	6
Decyl pentanoate	3
Unsaponifiables 1	2
Beeswax	3
PEG-2 stearate	1
C12-15 alcohol benzoate	1
Phenonip	0.7
Sepigel 305	0.5
TOTAL	100%

1.3) Composition 1.3: Use of furan-containing lipids of avocado

5 An unsaponifiable material from avocado is prepared as described in patent FR-2 678 632. Its composition is as follows:

- polyhydroxylated fatty alcohols 24.3%
- furan-containing lipids 55.5%
- 10 - sterols 3.1%
- squalene 1.4%
- others 15.7% (1)
- (1) free fatty acids, hydrocarbons, tocopherols, fatty ketones and heavy pigments

15

This unsaponifiable material is subjected to molecular distillation using the scraped-film molecular distillation machine sold by the company Leybold under the name "KDL4". The distillation conditions are as follows:

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- hot-surface temperature: 108°C
- pressure: 10^{-3} mmHg
- rotation speed of the shaft: 240 rpm
- flow rate of unsaponifiable material from
- 25 avocado: 400 ml/h

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Yield of distillate: 48.6%

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Composition of the distillate:

- polyhydroxylated fatty alcohols: n.m.
- furan-containing lipids 99.1%
- sterols n.m.
- squalene n.m.
- others 0.9% (1)

(1) free fatty acids, hydrocarbons and fatty ketones

("n.m.": not measurable, that is to say a content of less than 0.05%)

This is thus a distillate that is very rich in furan-containing lipids since the content of said lipids exceeds 99%. This distillate is referred to hereinbelow as "lipids 1"

Composition 1.3 (INCI names)	% (by weight)
Aqueous phase	
Water	69
Glycerol	4
Fatty phase	
Sorbitan tristearate	1.85
PEG-40 stearate	3.15
Silicone SF 1202	3
Cetiol Oe	1
Petroleum jelly codex	2.5
Glyceryl stearate	6
Decyl pentanoate	3
Lipids 1	0.3
Beeswax	3
PEG-2 stearate	1
C12-15 alcohol benzoate	1
Phenonip	0.7
Sepigel 305	0.5
TOTAL	100%

1.4) Placebo composition

Placebo composition (INCI names)	% (by weight)
Aqueous phase	
Water	69.3
Glycerol	4
Fatty phase	
Sorbitan tristearate	1.85
PEG-40 stearate	3.15
Silicone SF 1202	3
Cetiol Oe	1
Petroleum jelly codex	2.5
Glyceryl stearate	6
Decyl pentanoate	3
Beeswax	3
PEG-2 stearate	1
C12-15 alcohol benzoate	1
Phenonip	0.7
Sepigel 305	0.5
TOTAL	100%

5 **Example 2: in vitro evaluation of the effect of compositions 1.1, 1.2, 1.3 and placebo on the metabolism of the epidermal lipids in an organotypical model of whole human skin in culture**

10 The following abbreviations are used in the text hereinbelow:

EGF: epidermal growth factor;
 TLC: thin layer chromatography;
 15 MCF: culture medium for disks of human skin;
 MIF: incubation medium for disks of human skin;
 PBS: phosphate-buffered saline.

5 The study is performed *in vitro* in an organotypical model of whole human skin in culture. Two techniques successively used:

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1) Materials and method

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Compositions 1.1, 1.2, 1.3 and placebo were prepared as described above. The EGF was obtained from R&D Systems. The cosmetic formulation containing lactic acid,

The human skin disks are incubated in the presence of the test products and the reference products for 18

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hours at 37°C in a humid atmosphere containing 5% CO₂.

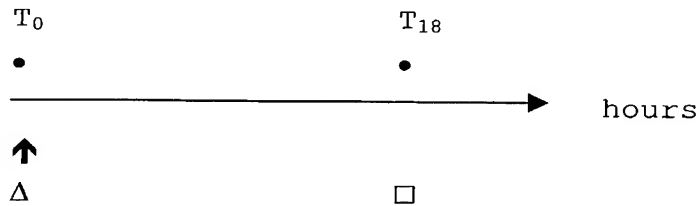
Control skin disks are incubated in parallel in the presence of test products and reference products.

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Each experimental condition is performed in quadruplicate.

The following time scale is used:

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↑ : topical application of the test products and the reference products and dilution of the EGF in the incubation medium for the skin disks

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Δ : addition of acetate labeled with carbon 14 to the culture medium

□ : dermal/epidermal dissociation and evaluation of the effects

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1.4) Evaluation of the effects

1.4.1) Neosynthesis of the total epidermal lipids

At the end of the incubation, the human skin disks are rinsed thoroughly with PBS buffer. The epidermis of each skin disk is dissociated from the dermis by means of a controlled heat shock (MilliQ water, 2 min, 62°C). The epidermises thus dissociated are digested with trypsin (ICN, 1%, w/v) overnight at 37°C. The cell dissociation is facilitated by the action of ultrasound.

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The neosynthesized lipids, labeled with carbon 14, are extracted by partition between an organic phase (1/4 methanol/chloroform, v/v) and an aqueous phase (0.25M potassium chloride). The organic phase is
5 evaporated under nitrogen and the residues are taken up in a 2/1 chloroform/methanol mixture (v/v).

The radioactivity of each sample, corresponding to the amount of acetate incorporated into the neosynthesized
10 lipids, is measured by liquid scintillation.

The results are expressed in cpm/mg of epidermis.

1.4.2) Nature of the neosynthesized epidermal lipids
15 Starting with the samples of extracted lipids, 20 µl aliquots, corresponding to 3 700 cpm, are placed on silica 60 (Merck) chromatography plates. These plates are developed in three successive solvents:

- 38/2/10 chloroform/acetone/methanol (v/v/v),
- 20 - 40/5/5 chloroform/acetone/methanol (v/v/v),
- 36/10/3/1 chloroform/ethyl acetate
/ether/methanol (v/v/v/v).

This system makes it possible to separate the
25 cholesteryl sulfate, the cerebroside, the ceramides, the cholesterol and the tri- + diglycerides. The most polar lipids, referred to hereinbelow as "polar lipids", remain on the base line.

30 The silica plates are then placed in exposure with films for autoradiography for 15 days (Amersham, Hyperfilm beta max).

The position of the various classes of lipids - polar
35 lipids, cholesteryl sulfate, cerebroside, ceramides 1 and 2, cholesterol and tri- + diglycerides - is determined using suitable standards.

The radioactivity of the spots separated and revealed by means of autoradiography is counted using a thin-film argon-methane radioactivity analyzer (Berthold). The results are expressed as percentages of the radioactivity of the total lipids neosynthesized and deposited on the TLC.

1.5) Treatment of the data

The groups of data (control group and treated groups) are compared by means of a one-factor analysis of variance (Anova 1, $p < 0.05$), followed by a Dunnett test.

2) Results

After incubating overnight in the presence of the human skin disks, the test compositions and the reference compositions have no significant effect on the neosynthesis of the total epidermal lipids (table 3.1). On the other hand, they appreciably modify the proportion of the various epidermal lipids in this total:

- **EGF** at 10 ng/ml reduced the neosynthesis of cholesteryl sulfate by 46% and increased the neosynthesis of ceramide 2 by 55% (table 3.2);
- **lactic acid** increases the neosynthesis of the cerebroside by a factor of 1.59 (table 3.2);
- **composition 1.1** increases the respective neosynthesis of ceramides 1 and 2 by a factor of 2.26 and 4.61, and the neosynthesis of cholesterol by a factor of 5.04. It reduces the neosynthesis of the tri- and diglycerides by 73% (table 3.3);
- **composition 1.2** increases the neosynthesis of cholesteryl sulfate by a factor of 1.32, the respective neosynthesis of ceramides 1 and 2 by a factor of 2.47 and 2.51, and the neosynthesis of cholesterol by a factor of 4.62. It reduces the neosynthesis of the tri- and diglycerides by 77% (table 3.2);
- **composition 1.3** increases the neosynthesis of

- 25 -

cholesteryl sulfate by a factor of 1.24, the
respective neosynthesis of ceramides 1 and 2 by a
factor of 1.59 and 3.66, and the neosynthesis of
cholesterol by a factor of 4.14. It reduces the
5 neosynthesis of the tri- and diglycerides by 84%
(table 3.2);

- **the placebo composition** reduces the neosynthesis
of the tri- and diglycerides by 59% (table 3.3)
without causing a significant increase in the
10 various epidermal lipids analyzed.

In conclusion, under the experimental conditions
adopted, compositions 1.1, 1.2, 1.3 and placebo have no
significant effect on the neosynthesis of the total
15 epidermal lipids.

On the other hand, they significantly modify the
proportion of the various classes of epidermal lipids
separated by thin layer chromatography in the *total*.

20 They reduce the neosynthesis of the tri- and
diglycerides to the benefit of the other epidermal
lipids.

25 Composition 1.1 increases the neosynthesis of
cholesterol (without modifying the neosynthesis of
cholesteryl sulfate) and the neosynthesis of the
ceramides.

30 Compositions 1.2 and 1.3 increase the neosynthesis of
cholesteryl sulfate and cholesterol, and the neo-
synthesis of the ceramides.

The placebo composition does not bring about a
35 significant increase in the various epidermal lipids
analyzed.

3) Tables of results

5 Table 3.1): Effect of compositions 1.1, 1.2, 1.3 and placebo and also of EGF and of a cosmetic formulation containing lactic acid on the neosynthesis of the total epidermal lipids in disks of whole human skin, after incubation for 18 hours

Control	EGF 10 ng/ml	Lactic acid	Compo- sition 1.2	Compo- sition 1.3	Compo- sition 1.1	Placebo compo- sition
4183.35	3104.63	1864.31	2479.26	3646.42	873.10	1506.12
4407.89	5043.66	4919.12	3858.70	5255.70	3726.00	4154.88
3691.69	3606.76	4027.67	6571.13	3900.53	3802.63	4429.96
1062.72	4565.02	1076.21	2457.78	3209.16	905.55	2373.94
3336.41	4080.02	2971.83	3841.72	4002.95	2326.82	3116.23
+/-	+/-	+/-	+/-	+/-	+/-	+/-
1545.02	883.02	1800.62	1934.04	882.63	1660.22	1408.09
<i>100</i>	<i>122</i>	<i>89</i>	<i>115</i>	<i>120</i>	<i>70</i>	<i>93</i>

- 10 The results are expressed in cpm/mg of epidermis
 In bold: mean and standard deviation
 In italics: percentage of the control group
 *: mean significantly different from the control group
 (p<0.05)

Table 3.2): Effect of compositions 1.2 and 1.3 and also of EGF and of a cosmetic formulation containing lactic acid on the neosynthesis of the polar lipids, of cholesteryl sulfate, of the cerebrosides, of ceramides 1 and 2, of cholesterol and of the tri- + diglycerides in disks of whole human skin, after incubation for 18 hours

Product	Polar lipids	Cholesteryl sulfate	Cerebrosides	Ceramide 1	Ceramide 2	Cholesterol	Tri- + di-glycerides
Control	28.94	6.04	1.89	2.03	2.03	8.23	50.83
	24.96	4.80	2.08	2.67	2.07	5.04	53.76
	31.74	6.26	4.02	2.71	2.15	7.89	45.23
	42.90	5.12	4.44	1.67	1.47	5.61	38.84
	32.14	5.56	3.11	2.27	1.93	6.69	47.17
	+/-	+/-	+/-	+/-	+/-	+/-	+/-
	7.70	0.71	1.31	0.51	0.31	1.60	6.58
EGF 10 ng/ml	100	100	100	100	100	100	100
	57.27	2.31	2.87	2.02	3.81	7.07	42.67
	34.42	3.69	3.82	1.41	2.38	9.46	44.82
	27.69	3.44	4.77	3.41	2.74	7.86	50.08
	33.53	2.57	4.02	4.02	3.05	9.99	42.83
	38.23	3.00*	3.87	2.72	3.00*	8.60	45.10
	+/-	+/-	+/-	+/-	+/-	+/-	+/-
	13.04	0.67	0.78	1.21	0.61	1.36	3.46
	119	54	125	120	155	128	96

Product	Polar lipids	Cholesteryl sulfate	Cerebrosides	Ceramide 1	Ceramide 2	Cholesterol	Tri- + di-glycerides
Lactic acid	49.20	4.07	4.46	2.37	1.70	7.77	33.43
	33.04	4.16	4.54	2.64	3.32	9.72	42.58
	64.49	5.90	6.07	2.94	2.57	8.07	31.95
	53.51	4.25	4.68	2.58	1.44	8.67	24.86
	50.06	4.60	4.94*	2.63	2.26	8.56	33.21
	+/-	+/-	+/-	+/-	+/-	+/-	+/-
	13.05	0.87	0.76	0.24	0.86	0.86	7.28
Composition 1.2	156	83	159	116	117	128	70
	24.57	6.89	4.41	2.78	6.86	44.35	10.13
	28.71	8.34	5.91	5.94	3.34	35.04	12.72
	33.09	6.86	4.02	4.55	4.79	36.97	9.72
	35.78	7.35	7.76	9.20	4.37	34.01	11.52
	30.54	7.36*	5.53	5.62*	4.84*	37.59*	11.02*
	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Composition 1.3	4.93	0.69	1.70	2.72	1.48	4.67	1.37
	95	132	178	247	251	562	23
	38.88	6.23	6.23	3.20	8.92	28.63	7.92
	43.70	8.25	4.55	3.51	7.25	24.34	8.41
	37.70	6.88	3.97	3.52	6.69	33.55	7.68
	47.94	6.15	6.13	4.24	5.40	24.30	5.85
	42.06	6.88*	5.22	3.62*	7.07*	27.71*	7.47*
	+/-	+/-	+/-	+/-	+/-	+/-	+/-
	4.70	0.97	1.13	0.44	1.46	4.39	1.12
	131	124	168	159	366	414	16

The results are expressed as a percentage of the radiolabeled total lipids applied onto the TLC.

In bold: mean and standard deviation

In italics: percentage of the control group

+: mean significantly different from the control group ($p < 0.05$)

14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

Product	Polar lipids	Cholesteryl sulfate	Cerebrosides	Ceramide 1	Ceramide 2	Cholesterol	Tri-diglycerides	+
Placebo composition	73.67	9.27	7.69	2.44	2.05	3.03	18.60	
	58.70	11.03	7.60	2.51	3.39	3.71	13.07	
	55.90	6.63	3.71	4.21	3.67	8.66	17.20	
	63.39	5.69	4.48	4.17	3.35	4.93	27.98	
	62.92	8.16	5.87	3.33	3.12	5.08	19.21*	
	+/-	+/-	+/-	+/-	+/-	+/-	+/-	
	7.81	2.44	2.07	0.99	0.72	2.51	6.30	
	196	147	189	147	161	76	41	

The results are expressed as a percentage of the radiolabeled total lipids applied onto the TLC.
 In bold: mean and standard deviation
 In italics: percentage of the control group
 +: mean significantly different from the control group ($p < 0.05$)

XXXXXXXXXXXXXXXXXXXX

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Example 3: Composition of a cream for atopic skin

INCI formulation		%
Water	qs	100
Glycerol		15
Petrolatum		2
Hydrogenated palm kernel oil		5
Caprylic/capric triglycerides		5
Cyclomethicone		1
Sucrose distearate		4
Dextrin		3
Sunflower (Helianthus annuus) seed oil		
unsaponifiables (1)		1
Squalane		2
Candelilla (Euphorbia cerifera) wax		1
Sucrose stearate		2
Oat (Avena sativa) flour		1
Dimethiconol		0.2
Methylparaben		0.4
Propylparaben		0.3
Xanthan gum		0.2
Ceramide 3		0.2
Total:		100%

5 (1): Sunflower oil distillate 1 of example 1

Example 4: Composition of a bath oil for atopic skin

INCI formulation	%
Sunflower (Helianthus annulus) seed oil	100
Octyl cocoate	15
Sweet almond (Prunus amygdalus dulcis) oil	15
Mineral oil	1
PEG-6 isostearate	5
Sunflower (Helianthus annuus) seed oil	
unsaponifiabiles (1)	60
Chamomile (Anthemis nobilis) oil	5
Propylene glycol dipelargonate	1
Lecithin	1
Laureth-2	0.5
Tocopherol	0.5
Ascorbyl palmitate	0.06
Total:	100%

(1): Sunflower oil distillate 1 of example 1

Example 5: Clinical study to evaluate the care effect of composition 1.1 of example 1 and checking of its satisfactory local skin tolerance, under dermatological control, after single and repeated applications for 4 weeks, on an "atopic" adult volunteer

1) Materials and method

1.1 Aim of the study

10 The aim is firstly to evaluate the care effect of a cosmetic product, by various biometrological measurements combined with clinical evaluations, and secondly to check their satisfactory local skin tolerance, after single and repeated cutaneous
15 applications for 4 weeks, on an "atopic" adult volunteer with very dry and squamous body skin.

1.2 Relevance of the test

"Double-blind" evaluations, based on:

- 20 - the principles of electrical conductivity of the skin, widely described for determining the state of moisturization of the upper layers of the epidermis (Tagami H. et al., 1980; Korstanje et al., 1992);
- 25 - the principle of photometry (sebumetric measurements), for evaluating the relipidizing effect of a cosmetic product;
- analysis by optical microscopy of surface "biopsies", performed by stripping, using
30 cyanoacrylate adhesive, making it possible to determine the effect of a cosmetic product on the "MicroDepression Network" (MDN);
- a clinical evaluation by the Study Director, a self-evaluation by the panelist and a
35 questionnaire.

1.3 Inclusion criteria

"Atopic" volunteer with dry to very dry and slightly

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5 followed by analysis by optical microscopy, on semi-structured linear scales of 12 cm, taking into account the cleanliness of the Microdepression Network and the surface appearance, before and then after the 4 weeks of applications;

- clinical evaluation by the Study Investigator and self-evaluation by the panelists of the "dryness", the "roughness" and the "desquamation" of the skin, on the basis of clinical scores or of analogue visual scales, at the same times as previously;
- assessment of the local skin tolerance of the product by the Dermatologist, after the 4 weeks of use;
- temperature and relative humidity regulated and checked at each testing time ($T^{\circ} = 22 \pm 2^{\circ}\text{C}$ and $\text{RH} = 50 \pm 5\%$).

20 1.7 Statistics

Instrumental measurements (corneometry and sebumetry): ANOVA and multiple-comparisons test ($p < 0.05$) relating to the absolute values and to the differences ($\Delta \text{Tx}-\text{T0}$).

25 MDN, analogue scales and clinical scores: Wilcoxon test in paired series ("two-tail", $p < 0.05$).

30 Calculation of the percentages of variation of the parameters evaluated during the study.

2) Results

35 2.1 EFFECT ON THE LEVEL OF SURFACE SKIN LIPIDS AFTER SINGLE APPLICATION (Sébumètre™)

A statistically significant increase in the level of surface skin lipids relative to the initial

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measurements and to the values recorded on the control area, 1 and then 2 and 3 hours approximately after the first application, are found, reflecting an immediate marked relipidizing effect, not revealed approximately 24 hours after the application (reflecting a total absorption of composition 1.1, without the presence of a residual greasy film on the surface of the skin).

2.2 EFFECT ON THE DEGREE OF MOISTURIZATION OF THE UPPER LAYERS OF THE EPIDERMIS AFTER SINGLE AND REPEATED APPLICATIONS (Cornéomètre™)

- After single application (n = 20)

A statistically significant increase in the electrical capacitance is found relative to the initial measurements and to the measurements recorded on the control area, 1 and then 2, 3 and 24 hours approximately after the first application of composition 1.1.

- After 4 weeks of repeated use (n = 18)

A statistically significant increase in the electrical capacitance relative to the initial measurements is found.

TABLE 5.1

GAINS IN MOISTURIZATION	Control area	COMPOSITION 1.1 (EXAMPLE 1)
T 1 hour	+ 0.0%	+ 48.6%°
T 2 hours	+ 1.0%	+ 58.7%°
T 3 hours	+ 0.5%	+ 64.4%°
T 24 hours	+ 2.9%	+ 34.2%°
T 4 weeks		+ 22.4%°

°: statistically significant increase in comparison

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with the untreated control area

2.3 EFFECT ON THE MICRODEPRESSION NETWORK

(analysis by optical microscopy of surface "biopsies":
12 cm semi-structured linear scales)

A statistically significant restructuring of the MicroDepression Network is found, after 4 weeks of application.

TABLE 5.2

	COMPOSITION 1.1 (EXAMPLE 1)
Microrelief	+ 10%
Surface appearance	+ 52%

2.4 CLINICAL EVALUATION BY THE STUDY DIRECTOR (g-point clinical scores)

A statistically significant variation in the following judgement criteria is observed, after 4 weeks of application:

TABLE 5.3

	COMPOSITION 1.1 (EXAMPLE 1)
Skin dryness	-54% ($p = 0.0002$)
Skin roughness	-52% ($p = 0.0002$)
Desquamation	-54% ($p = 0.0004$)

2.5 SELF-EVALUATION BY THE VOLUNTEERS

(10-point analogue visual scales)

A statistically significant variation in the following judgement criteria is observed, after 4 weeks of application:

TABLE 5.4

	COMPOSITION 1.1 (EXAMPLE 1)
Skin dryness	-60% ($p = 0.0002$)
Skin roughness	-55% ($p = 0.0002$)
Desquamation	-60% ($p = 0.0002$)

3) Conclusion

In conclusion, the single application to the skin of composition 1.1 to 20 "atopic" female adult volunteers with dry to very dry skin, in comparison with an untreated control area (under double-blind conditions), resulted in:

- a statistically significant effect on the content of surface skin lipids (photometric measurements), in comparison with an untreated control area, reflecting a marked immediate relipidizing effect, not revealed 24 hours approximately after the application, reflecting a total absorption of the product, without the presence of a residual greasy film on the surface of the skin;
- a marked effect on the degree of moisturization of the upper layers of the epidermis (electrical capacitance measurements), 1, 2, 3 and 24 hours approximately after the application, reflecting an

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excellent remanence.

The repeated applications, twice a day for 4 consecutive weeks, under the normal conditions for use, by a panel of 18 adult female individuals, moreover, resulted in:

- a statistically significant effect on the degree of moisturization of the upper layers of the epidermis;
- a statistically significant restructuring of the microdepression network;
- a statistically significant improvement in the appearance of the skin (dryness, roughness and desquamation).

A positive judgement was also given by the majority of the panelists for the efficacy of composition 1.1 as a "care cream for dry skin", and also for its cosmetic qualities.

The applications of the studied composition 1.1 were found, moreover, to be very well tolerated.

This set of results thus makes it possible to justify, for composition 1.1, the following properties:

- an immediate relipidizing effect,
- an immediate and long lasting moisturizing effect on the upper layers of the epidermis,
- an improvement in the appearance of the skin, and
- a tolerance and efficacy tested under dermatological monitoring.

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AMENDED CLAIMS

[received by the International Office on 16 February 2001 (16.02.01); claims 1 to 33 replaced by new claims 1 to 31 (4 pages)]

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1. The use of at least one plant oil product chosen from the group consisting of oil distillates of plant oil, unsaponifiable materials from plant oil, furan lipids of plant oil and mixtures thereof for the preparation of a composition containing a cosmetically, pharmaceutically or dermatologically acceptable medium.
2. The use as claimed in claim 1, characterized in that the skin lipids are chosen from the epidermal lipids of the group consisting of cholesterol, cholesteryl sulfate, ceramides 1 and 2 and mixtures thereof.
3. The use as claimed in claim 1 or 2, characterized in that the unsaponifiable materials and the oil distillates of plant oil are chosen from the group consisting of unsaponifiable materials and oil distillates that are rich in tocopherols and/or in phytosterols.
4. The use as claimed in any one of the preceding claims, characterized in that the oil distillates of plant oil are oil distillates of sunflower oil.
5. The use as claimed in any one of the preceding claims, characterized in that the unsaponifiable materials from plant oil are unsaponifiable materials from avocado or from soybean, or mixtures thereof.
6. The use as claimed in any one of the preceding

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- claims, characterized in that the unsaponifiable material from plant oil is a mixture of unsaponifiable material from avocado oil and of unsaponifiable material from soybean oil, the weight ratio of unsaponifiable material from avocado oil to the unsaponifiable material from soybean oil being between about 0.1 and about 9.
7. The use as claimed any one of the preceding claims, characterized in that the furan lipids of plant oil are furan lipids of avocado.
 8. The use as claimed in any one of the preceding claims, characterized in that the plant oil product is used in a proportion of between about 0.01% and 100% by weight relative to the total weight of the composition.
 9. The use as claimed in any one of the preceding claims, characterized in that the composition contains a cosmetically, pharmaceutically or dermatologically acceptable medium.
 10. The use as claimed in any one of the preceding claims, characterized in that the cosmetically, pharmaceutically or dermatologically acceptable medium is an oily solution, a water-in-oil emulsion, an oil-in-water emulsion, a micro-emulsion, an oily gel, an anhydrous gel or a dispersion of vesicles, microcapsules or microparticles.
 11. The use as claimed in any one of the preceding claims, characterized in that the composition is for topical application.
 12. The use as claimed in any one of claims 1 to 11, characterized in that the composition is intended

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for treating dry skin.

13. The use as claimed in any one of claims 1 to 11,
characterized in that the composition is intended
for treating skin that has been subjected to
actinic radiation, especially UV radiation.

14. The use as claimed in any one of claims 1 to 11,
characterized in that the composition is intended
for treating ichthyosis.

15. The use as claimed in any one of claims 1 to 11,
characterized in that the composition is intended
for treating acne.

16. The use as claimed in any one of claims 1 to 11,
characterized in that the composition is intended
for treating xerosis.

17. The use as claimed in any one of claims 1 to 11,
characterized in that the composition is intended
for treating atopic dermatitis.

18. The use as claimed in any one of claims 1 to 11,
characterized in that the composition is intended
for treating skin disorders associated with a
reduction in the content of skin lipids,
especially the lipids of the epidermal skin
barrier.

19. The use as claimed in any one of claims 1 to 11,
characterized in that the composition is intended
for treating sensitive skin.

20. The use as claimed in any one of claims 1 to 11,
characterized in that the composition is intended
for treating irritated skin.

21. The use as claimed in any one of claims 1 to 11,

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AMENDED PAGE (ARTICLE 19)

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characterized in that the composition is intended for treating reactive skin.

- 5 22. The use as claimed in any one of claims 1 to 11, characterized in that the composition is intended for treating disorders of corneocyte cohesion.
- 10 23. The use as claimed in any one of claims 1 to 11, characterized in that the composition is intended for treating desquamation of the skin.
- 15 24. The use as claimed in any one of claims 1 to 11, characterized in that the composition is intended for treating pruritus.
- 20 25. A method for cosmetic treatment of disorders associated with aging of the skin, neighboring mucous membranes and/or integuments, characterized in that a composition containing at least one plant oil product as defined in any one of claims 1 to 7, in a cosmetically acceptable medium, is applied to the skin, neighboring mucous membranes and/or integuments, so as to increase the synthesis of the skin lipids, especially of the lipids of the epidermal skin barrier.
- 25 26. A method for cosmetic treatment of disorders associated with drying of the skin, neighboring mucous membranes and/or integuments, characterized in that a composition containing at least one plant oil product as defined in any one of claims 1 to 7, in a cosmetically acceptable medium, is applied to the skin, neighboring mucous membranes and/or integuments, so as to increase the synthesis of the skin lipids, especially the lipids of the epidermal skin barrier.
- 30 27. A method for cosmetic treatment of disorders of
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the skin, mucous membranes and/or integuments, resulting from an exposure to actinic radiation, especially UV radiation, characterized in that a composition containing at least one plant oil product as defined in any one of claims 1 to 7, in a cosmetically acceptable medium, is applied to the skin and/or integuments, so as to increase the synthesis of the skin lipids, especially the lipids of the epidermal skin barrier.

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28. The cosmetic treatment method as claimed in any one of claims 25 to 27, characterized in that the plant oil product is present in the composition in a proportion of between about 0.01% and 100% by weight relative to the total weight of the composition.

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29. The cosmetic treatment method as claimed in any one of claims 25 to 28, characterized in that the cosmetically acceptable medium is as defined in claim 10.

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30. The use of at least one plant oil product as defined in any one of claims 1 to 7, in a food for humans and/or animals as an additive acting to increase the synthesis of the skin lipids, especially the lipids of the epidermal skin barrier.

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31. The use as claimed in claim 30, characterized in that the plant oil product is present in the food in a proportion of between about 0.1% and about 20% by weight relative to the total weight of the food.

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(54) Title: USE OF A VEGETABLE OIL PRODUCT AS AGENT FOR INCREASING SKIN LIPID SYNTHESIS

(54) Titre: UTILISATION D'UN PRODUIT D'HUILE VÉGÉTALE EN TANT QU'AGENT POUR AUGMENTER LA SYN-
THÈSE DES LIPIDES CUTANÉS

(57) Abstract: The invention concerns the use of at least a vegetable oil product selected among the group consisting of vegetable oil oleic distillates, vegetable oil unsaponifiable matters, vegetable oil furan lipids and mixtures thereof, as agents for increasing skin lipid synthesis, in particular lipids of the epidermal skin barrier, in or for preparing a composition containing a pharmaceutically or dermatologically acceptable medium. The use enables to prevent and/or treat deterioration of the skin barrier (dry skin, skin subjected to actinic radiation, ichthyosis, acne, xerosis, atopic dermatitis, sensitive skin, chafing and reactive skin, itching and the like)

(57) Abrégé: La présente invention se rapporte à l'utilisation d'au moins un produit d'huile végétale choisi dans le groupe constitué par les oléodistillats d'huile végétale, les insaponifiables d'huile végétale, les lipides furaniques d'huile végétale et les mélanges de ces derniers, en tant qu'agent pour augmenter la synthèse des lipides cutanés, notamment des lipides de la barrière cutanée épidermique, dans ou pour la préparation d'une composition contenant un milieu cosmétiquement, pharmaceutiquement ou dermatologiquement acceptable. L'utilisation selon l'invention permet de prévenir et/ou de traiter les altérations de la barrière cutanée (peaux sèches, peaux ayant été soumises à un rayonnement actinique, ichtyose, acné, xérose, dermatite atopique, peaux sensibles, irritées et réactives, prurit, etc.).

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

ATTORNEY'S DOCKET NO.: REGIM-012

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: USE OF A PLANT OIL PRODUCT AS AN AGENT FOR INCREASING THE SYNTHESIS OF SKIN LIPIDS

the specification of which is attached hereto

☒ was filed on September 20, 2000
Number PCT/FR00/02600

as

PCT International Application
and was amended on February 16, 2001 (if applica

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35i United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (month, day, year)	PRIORITY CLAIMED
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			YES <input type="checkbox"/> NO <input type="checkbox"/>
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LISTING OF FOREIGN APPLICATIONS CONTINUED ON PAGE 3 HEREOF <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO			

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

Application Number: _____ Filing Date: _____

Application Number: _____ Filing Date: _____

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

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PCT Parent Number: _____ Parent Filing Date: _____

LISTING OF US APPLICATIONS CONTINUED ON PAGE 3 HEREOF: ☐ YES ☒ NO

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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DECLARATION -- Page 2

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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